It was a real pleasure to host the 14th Annual Scrip Awards, in conjunction with IQVIA, and honor the achievements of the pharmaceutical, biotech, clinical research and allied sectors.

Those in the industry know that R&D innovation is driving more activity in the sector than ever before. As biosimilars gradually increase their place on the market and payers worldwide demand price restraints, we’ve seen industry renewal through the development and launch of a number of new therapy modes that truly offer tremendous value to patients and society, from gene and cell therapies to continuing advances in immuno-oncology. With data and artificial intelligence tools helping to drive transformation across the industry’s activities, the future is bright for biopharma.

In such a time of change, it is worth stepping back to recognize the exceptional accomplishments of an industry that rises to the formidable challenge of improving human health. Awards presented at acknowledged the industry’s perseverance in the face of apparently intractable complexity that continues to yield medical breakthroughs. The Scrip Awards celebrate industry’s ingenuity and diligence in making treatments widely available to patients which directly improves the quality and length of people’s lives.

Thanks to all of you who entered – being on the shortlist was a real achievement and our judges had the difficult task of in deciding the winners from an impressive line-up of entrants. The awards cover the whole spectrum of business activities, from new product launches to clinical trials, fundraising and deals, while also recognizing the leadership and teamwork that these require.

Many of these achievements in deals, R&D and fundraising have been documented by Scrip over the past 12 months or so. Please enjoy the selection of recent articles that reflect the wide array of industry activities and the breadth of our coverage.

Eleanor Malone
Editor in Chief, Scrip
Pharma Intelligence
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The winners of the 14th Annual Scrip Awards were announced 28 November at The Hilton on Park Lane.

We’d like to take this opportunity to thank everyone who entered and congratulations to the winners.

THE 2018 SCRIP AWARDS WINNERS

MEDIDATA
Medidata Rave Engage
BEST TECHNOLOGICAL DEVELOPMENT IN CLINICAL TRIALS - TECH SPONSOR-FOCUSED

COVANCE
Xcellerate CRA Dashboard
BEST TECHNOLOGICAL DEVELOPMENT IN CLINICAL TRIALS - CLINICAL SPONSOR-FOCUSED

PAREXEL, EMD SERONO AND INTERMOUNTAIN HEALTHCARE
International’s Multiple Sclerosis Algorithms Development and Validation project
BEST USE OF REAL-WORLD EVIDENCE

BIONTECH
$270m Series A financing
FINANCING DEAL OF THE YEAR – PRIVATE

ABLYNX
$200m US IPO on NASDAQ
FINANCING DEAL OF THE YEAR – PUBLIC

F-STAR AND DENALI THERAPEUTICS
Developed a multi-specific platform for delivery of medicines across the blood-brain barrier
BEST PARTNERSHIP ALLIANCE
CYTEL
BEST CONTRACT RESEARCH ORGANIZATION – SPECIALIST PROVIDERS

IQVIA
BEST CONTRACT RESEARCH ORGANIZATION – FULL-SERVICE PROVIDERS

EVOtec
business development team
BUSINESS DEVELOPMENT TEAM OF THE YEAR

WUXI BIOLOGICS
Masters Specialty Pharma’s Best Company in an Emerging Market Award

ASTRAZENECA AND MSD
For Lynparza and selumetinib
Licensing Deal of the Year – Sponsored by Worldwide Clinical Trials

RAMAN SINGH
CEO of Mundipharma
Executive of the Year – For Small Cap & Private Pharma Companies

VAS NARASIMHAN
CEO of Novartis
Executive of the Year – For Large & Medium Cap Companies

GW PHARMACEUTICALS
Phase III GWPCARE4 trial of Epidiolex for refractory epilepsy
IQVIA’s Clinical Advance of the Year Award

BEXIMCO PHARMA WITH DSM NUTRITIONAL PRODUCTS AND SIGHT & LIFE GLOBAL NUTRITION RESEARCH INSTITUTE
To improve nutrition in rural Bangladesh
Community Partnership of the Year Award – Sponsored by Medidata Solutions

AVEXIS
WUXI APPTec’s Biotech Company of the Year Award

NOVARTIS AND KITE PHARMA/GILEAD SCIENCES
Novartis’s Kymriah (tisagenlecleucel) and Kite Pharma/Gilead Sciences’ Yescarta (axicabtagene ciloleucel)
Syneos Health’s Best New Drug Award

MSD
Pharma Company of the Year

SIR JOHN BELL
SCRIP’s Lifetime Achievement Award
Scrip is pleased to announce, with sponsorship from MSD, the creation of the MSD Innovation Award.

This new category will acknowledge and celebrate the outstanding scientific or technological breakthrough that the judging panel believes has the potential to be transformative in the discovery or development of new medicines.

The award is open to any person, group or company that has achieved a genuinely ground-breaking advance during the qualifying period of June 1st 2018 to May 31st 2019. We welcome entries that are active in the life sciences ecosystem – from early-stage research through to clinical proof-of-concept developments.

Achievements we wish to recognize include: insights that advance our understanding of disease biology; new therapeutic targets or approaches; elucidation of a novel mechanism of action, clinical proof of concept of a novel mechanism or novel target, techniques and technology platforms that enhance the medical benefits of new or existing medicines;

Entries will be judged on the answers to a number of key questions:

- What is the scientific, technological or medical challenge they are targeting?
- What is the solution to the challenge?
- What proof of principle or concept have been achieved?
- How will the entry impact either the discovery or development innovative therapeutic approaches?
- How novel is the innovation?
- How well has the entrant elucidated the biology of the target, mechanism and/or its role in disease?
- What challenges still need to be resolved to fulfil the innovation’s potential?
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The Most Successful Oncology Launches Of A Decade

By Jessica Merrill

Cancer drugs launched over the last 12 years generated roughly $50bn in sales in 2017 and a cumulative $179bn during that time, highlighting just how important the therapeutic area is to the drug industry – and how pivotal it is poised to remain.

The investment banking firm Leerink analyzed 94 cancer drugs approved by FDA from 2006 to 2017, collecting information on the launch dates, indication and quarterly revenue performance (when publicly available) to determine which drugs were most commercially successful and which drug manufacturers stood out from the competition.

The most commercially successful new cancer drugs introduced in the 12-year period were Johnson & Johnson’s prostate cancer drug Zytiga (abiraterone) and Pfizer Inc.’s Sutent (sunitinib), approved for kidney cancer, pancreatic cancer and gastrointestinal stromal tumors (GIST), according to Leerink. Zytiga generated cumulative sales of $12.2bn over the period and Sutent generated $11.8bn.

The most commercially successful launches, however, were newer drugs – Bristol-Myers Squibb Co.’s immune checkpoint inhibitor Opdivo (nivolumab) and Pfizer’s CDK4/6 inhibitor for breast cancer Ibrance (palbociclib). In three years of cumulative sales, Opdivo generated $8.3bn and Ibrance generated $6bn, Leerink said.

In contrast, for the 50 drugs with at least three years of sales, the average one generated $152m in first-year sales, growing to $612m in year three. The top decile generated $493m in the first year, growing to $2.88bn in three years, while the bottom decile generated $11m in year one sales and $25m in year three. The US generally contributes 65% of revenue by year three post approval.

“It is also apparent that the most successful cancer drugs (top 10%) started off on the right foot and then grew much more rapidly than the other 90% afterwards, making the gap between them even wider over time,” the Leerink analysts said. Geoffrey Porges, Seamus Fernandez and Michael Schmidt conducted the analysis.

While Roche has had a long period of leadership in oncology, it wasn’t at the forefront of immuno-oncology. The success of Opdivo catapulted Bristol into the number one position in terms of cumulative worldwide sales of new cancer drugs between 2006 and 2017. “This makes Bristol the most commercially successful company in oncology, especially in the context of the immuno-oncology boom in recent years,” the analysts said. Novartis was second with the leukemia drug Tasigna (nilotinib) being the single biggest contributor to the cumulative sales.

Bristol and most companies (excluding Roche, Novartis AG and Pfizer) have their top 3 drugs accounting for over 90% of revenues generated from new cancer drugs.

“We think this reflects the wide gap between successful and ordinary cancer drugs as well as the difficulty for any company to identify and develop more than a couple of good drug candidates,” the analysts said.

Leerink pointed to one caveat in the analysis when it comes to the biotech Celgene Corp., because two of its blockbuster cancer drugs were approved in 2015 Revlimid (lenalidomide) and Abraxane (paclitaxel protein-bound) – and therefore did not make the approval cut-off of 2006 of FDA’s public archive. If Revlimid had been included, it would most likely be the best-selling cancer drug in the
The top two most successful oncology companies in terms of number of new molecular entities approved during the period were Roche and Novartis. Roche and Bristol stood out for having the most new indications approved. Roche launched nine new cancer drugs over the 12 years, while Novartis launched eight. Nonetheless, the analysts viewed Novartis’ portfolio as more innovative in that the products reflected multiple mechanism of action, while many of Roche’s new drugs were directed against targets like CD20 and HER2 that the company knows well.

“The approval pattern shows concentration of development successes in a few indications, which has led to intensified competition in those indications, while leaving many cancer types still in need of breakthrough treatment options,” Leerink analysts said. The most common indications for new drugs have been non-small cell lung cancer...
Top 10 Indications For Cancer Drugs Approved From 2006-2016

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Source: FDA.gov; Leerink Partners Research

(NSCLC), non-Hodgkin's lymphoma and breast cancer, consistent with the large addressable patient populations in those cancers and therefore the large commercial potential. Cancers with less activity include kidney cancer, head and neck cancer, bladder cancer, pancreatic cancer, colorectal cancer, gastric cancer and liver cancer, the authors pointed out.

Five EGFR inhibitors, four ALK inhibitors and three PD-1/L1 inhibitors have been approved for NSCLC in the last 12 years. “This is a prime example of rapid follow-on development leading to heightened competitive intensity in specific indications,” the analysts added.

The goal of the project, they said, was to assess the reliability of their financial forecasts and to consider whether other approaches might be more valuable than traditional patient-based forecasts. A follow up analysis will examine predictability of cancer drug revenue, they said.

Published online in Scrip, 28 February 2018
Masters Speciality Pharma - an Established Presence in the Emerging Markets of Latin America and the Middle East

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Masters Speciality Pharma is comprised of two divisions. Masters Speciality Access (MSA), founded 34 years ago with the objective of supplying high-quality, unlicensed medicines to patients and their healthcare providers in emerging markets. Masters Speciality Medicines (MSM) licenses and registers niche medicines guaranteeing a reliable, affordable local source of products in Oncology, Haematology, Orphan Diseases and Pain Management. Together, these divisions help Masters to achieve its vision of “Medicines Reaching Further”.

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Alexion is a global biopharmaceutical company focused on serving patients and families affected by rare diseases through the innovation, development and commercialization of life-changing therapies. Patients with rare diseases often have no effective treatment options, and they and their families suffer with little hope. Our goal is to deliver medical breakthroughs where none currently exist.
We are honored to be a finalist for the IQVIA’s Clinical Advance of the Year Award for our advancements in the treatment of generalized myasthenia gravis (gMG).

More than two decades ago, Alexion began researching the science of complement, and exploring the ways that complement inhibition could be used to treat rare and ultra-rare diseases – many of which have limited or no treatment options.

We have since advanced the understanding of complement therapeutics and produced the first new treatment in decades for a debilitating neuromuscular disorder that affects thousands of patients around the world.

As we celebrate this achievement, we remain focused on delivering the highest level of medical innovation in order to redefine the future for more patients and families suffering from rare diseases. Thank you again to Scrip for this great honor.
Merck’s Keytruda Enjoys Clean Sweep In Lung Cancer, At Bristol’s Expense

By Emily Hayes

Merck & Co. Inc.’s PD-1 inhibitor Keytruda has emerged as the clear winner in non-squamous non-small cell lung cancer (NSCLC), with consistent and striking survival data for the combination of the drug with chemotherapy in the Phase III KEYNOTE-189 study, leaving an uncertain future for Bristol-Myers Squibb Co.’s competing Opdivo/Yervoy combination.

On April 16, the American Association for Cancer Research (AACR) meeting featured full data from landmark studies in first-line metastatic NSCLC. Merck’s KEYNOTE-189 study compared Keytruda (pembrolizumab) with doublet chemotherapy – Eli Lilly & Co.’s Alimta (pemetrexed) and cisplatin or carboplatin vs. the chemo combo alone in non-squamous NSCLC – and Bristol’s CheckMate-227 study tested its PD-1 inhibitor Opdivo (nivolumab) with its CTLA-4 inhibitor Yervoy (ipilimumab) in squamous and non-squamous NSCLC.

There were some noteworthy differences in trial design. For example, crossover was permitted for placebo patients with verified disease progression in KEYNOTE-189, whereas no crossover was allowed between treatment groups in CheckMate-227.

Results for both trials were published the same day in the New England Journal of Medicine; positive top-line results had previously been released for both trials.

‘Absolutely’ Standard Of Care

The many positive data points across the board in KEYNOTE-189 included an overall survival (OS) benefit with a very strong hazard ratio of 0.49. This result was quite “extraordinary” and “exceeded expectations,” as a 0.70 or 0.75 hazard ratio on this endpoint would have been considered by experts to be a major advance, said Roy Herbst, chief of medical oncology at the Yale Cancer Center and Smilow Cancer Hospital, discussing results at the AACR meeting, being held April 14-18 in Chicago.

Noting that the overall survival data were positive across study groups regardless of PD-L1 expression, Herbst said that the Keytruda/chemo combination is “absolutely” now the standard of care in first-line, non-squamous NSCLC.

Bristol’s CheckMate 227 study is more complex in its design and interpretation. In February, the company announced that it had changed the design to feature progression-free survival (PFS) as a main efficacy measure in a subset of patients with a high level of tumor mutation burden, instead of using PD-L1 expression. (Also see “Bristol’s Opdivo/Yervoy Bid Will Show Whether Tumor Mutation Burden Is Ready For Prime Time” - Pink Sheet, 5 Feb, 2018.)

At the AACR meeting, the company reported that in patients with high tumor mutation burden, defined as 10 mutations per megabase, the median PFS was 7.2 months for Yervoy/Opdivo versus 5.5 months for pemetrexed with cisplatin or carboplatin, a statistically significant result, with a hazard ratio of 0.58. Overall survival data are not yet mature.

NSCLC is expected to account for close to half of the total immuno-oncology (IO) market and Keytruda secured the first and only monotherapy approval in first-line metastatic NSCLC in October 2016 in patients with at least 50% PD-L1 expression, adding to its approval in second-line NSCLC for all levels of expression. The combination of Keytruda and pemetrexed also secured FDA approval for first-line NSCLC. On April 9, the drug solidified its lead in NSCLC with data from the KEYNOTE-042 first-line lung cancer study supporting Keytruda as a monotherapy in patients with at least 1% PD-L1 expression. (Also see “Merck’s Keytruda Set For Expanded Use As Lung Cancer Monotherapy “ - Scrip, 10 Apr, 2018.)

Bristol’s Opdivo infamously failed as a monotherapy in first-line NSCLC in the CheckMate 026 study, which was stratified by PD-L1 expression, though a retrospective analysis showed a benefit for those with high TMB. (Also see “Does CheckMate 026 Take Bristol Out Of The End Game?” - Scrip, 5 Aug, 2016.)
Merck’s Lead Will Widen

Merck’s KEYNOTE-189 data are strong enough to support full regulatory approval in the US, Japan, and EU, and will continue to widen the first-line lead held by Keytruda, Datamonitor analyst Dustin Phan commented to Scrip. “At this point, Merck & Co appears to be the clear winner due to the availability of OS data for both single-agent Keytruda and Keytruda plus chemotherapy in the first-line setting,” Phan said.

Overall survival data from CheckMate-227 will be necessary to better understand the potential impact Opdivo plus Yervoy will have on treatment trends in first-line NSCLC, the analyst added. These data are expected at the end of 2018 or early 2019.

Performance Across PD-L1 Levels

Both Keytruda and Opdivo demonstrated performance across PD-L1 subgroups and good safety relative to the comparator arms.

The KEYNOTE-189 study included 616 patients with previously untreated metastatic NSCLC with all levels of PD-L1 expression and no EGFR or ALK mutations. (Also see “Merck Hits IO Bullseye With Keytruda Combo In First-line Lung Cancer” - Scrip, 16 Jan, 2018.) After a median 10.5 months follow-up, OS at 12 months was 69.2% for the Keytruda/chemo combination versus 49.4% for the placebo-controlled chemo comparator.

“Improvement in overall survival was seen in all PD-L1 categories that were evaluated,” Leena Gandhi, director of thoracic oncology at the Perlmutter Cancer Center at New York University, and colleagues reported in the NEJM.

Median PFS for the Keytruda arm was also superior at 8.8 months vs. 4.9 months.

Herbst said that for all endpoints and subgroups evaluated in the study, there were significant benefits except for PFS in patients with less than 1% PD-L1 expression, which is “cause for a little concern.” However, he added, overall survival was significantly better in this group and that trumps PFS.

“So this is something to keep in mind as we move forward but I don’t think it’s a major limitation of the study,” Herbst. Furthermore, safety was similar – the rate of severe adverse events (AEs) was 67.2% for the Keytruda arm vs. 65.8% for placebo. The KEYNOTE-189 investigators and Herbst both flagged the rate of acute kidney injury in the Keytruda/chemo arm (5.2% vs. 0.5%). “In the pembrolizumab-combination group, acute kidney injury was of grade 3 or higher in 8 patients (2.0%); at the time of this analysis, acute kidney injury of grade 3 or lower had resolved or was resolving in 9 of 19 patients,” the NEJM article states.

But the signal is not likely to be a deterrent, analysts concluded. “Safety was not an issue, except for the curious finding of more frequent kidney injury with chemo combo. On balance, the data is clean, except performance of the control arm was worse than historical precedent would have predicted, providing [Merck] with a beneficial tailwind,” Bernstein Research analyst Tim Anderson said in an April 16 note.

“The only drawback is that grade 3-5 AEs occurred in ~67% of both arms, but were mostly chemo related (nausea, anemia, fatigue). However, efficacy drives treatment choice. [Merck] can offer Keytruda + chemo in healthier patients, and Keytruda monotherapy in sicker patients,” BMO Capital Markets analyst Alex Arfaei said in an April 16 note.

Anderson said that the data confirm that Merck will remain in the driver’s seat in terms of IO penetration into the all-important first-line lung cancer market, which has been forecast to be worth $7.5bn by 2021, for the PD-1/L1 segment.

Herbst said that the study that had supported the accelerated approval of the combination in first-line NSCLC – KEYNOTE-21G – was small and consequently the regimen was not used as much as it could be, although Merck has had a strong launch into the first-line setting. (Also see “Merck’s Keytruda Claims Market Leadership In First-line Lung Cancer” - Scrip, 30 Jul, 2017.) “Everyone was waiting for the results we heard today,” he noted.

Merck Laboratories Chief Medical Officer Roy Baynes commented to Scrip that the study asked simple questions and was remarkably clean, with a high degree of consistency, “the mark of a robust trial.”

Like Herbst, Baynes expects an uptick in use.
“It’s clear that data does drive practice – as it should, because it’s good for patients,” Baynes said.

**Bristol Data Disappoints**

Bristol’s CheckMate 227 was a multi-arm study of 1,739 patients that randomized patients based on PD-L1 expression to treatment with Opdivo and a low dose of Yervoy (1 mg/kg), double platinum chemotherapy, Opdivo monotherapy or Opdivo/chemotherapy. (Also see “Bristol Debuts Opdivo/Yervoy Data In New First-Line Lung Cancer Bid” - Scrip, 5 Feb, 2018.) The study included all levels of PD-L1 expression but excluded patients with EGFR and ALK mutations.

Results were reported by Memorial Sloan Kettering oncologist Matthew Hellman and colleagues in the NEJM.

Bristol was originally going to evaluate efficacy based on performance in PD-L1 subsets but wound up pooling parts of the trial and using PFS in a subset with high TMB as a coprimary endpoint – 299 participants (130 on Opdivo/Yervoy and 160 on double chemotherapy). **Foundation Medicine Inc.’s** FoundationOne CDx assay was used to assess PD-L1 and tumor mutation burden in the study.

Those with higher tumor mutation burden (TMB ≥10 mut/Mb) had significantly longer PFS, with 42.6% alive at one year in the Opdivo/Yervoy arm, versus 13.2% for chemotherapy. The objective response rates (ORR) in these patients were 45.3% for Opdivo/Yervoy vs. 26.9% for chemotherapy.

The benefit for the IO combination was broadly consistent regardless of PD-L1 expression or histology (squamous vs. non-squamous), investigators reported.

The one-year PFS rate of about 13% is very low for chemo; in TMB-unselected patients one-year PFS with chemo ranges from 25%-35%, BMO Capital’s Arfaei commented.

Anderson commented that TMB is an emerging but still highly unconventional biomarker. “In ‘low TMB’ patients, the combination did worse than chemotherapy by itself. This is in stark contrast to MRK’s ‘189 data, whose combination did better than chemotherapy in all segments, and the magnitude of the benefit in all of these segments was impressive,” he said.

On the safety front, the rate of severe adverse events for Yervoy/Opdivo was 31.2% vs. 36.1% for chemotherapy.

**Merck On Top, As Expected**

Analysts also expressed concern about data from CheckMate 227’s Opdivo monotherapy arm.

“The Opdivo monotherapy section in the NEJM describes how mPFS with Opdivo monotherapy is essentially no better than chemotherapy by itself in PDL1+ patients using a TMB cutpoint at >13 [13 mutations per megabase]. It is difficult for us to interpret this data, but harkening back to the failed CM-026 study, it leaves open the possibility that Opdivo monotherapy may just not be as good as Keytruda monotherapy – for some unknown reason – a possibility we have often been dismissive of,” Anderson said.

Analysts had expected Merck to emerge in a better position relative to Bristol at the AACR meeting, with robust survival data from KEYNOTE-189, and believe it may be hard for Opdivo to rebound in the important lung cancer indication.

One consolation for Bristol is the April 16 approval by FDA of the Opdivo (3 mg/kg)/Yervoy (1 mg/kg) combination in first-line renal cell carcinoma patients at intermediate and poor risk (about 75% of the population). The combination had demonstrated an overall survival benefit regardless of PD-L1 expression in the CheckMate 214 study, which tested the regimen against Pfizer Inc.’s tyrosine kinase inhibitor Sutent (sunitinib). (Also see “Bristol’s Strong SITC: IDO, 1L Kidney Cancer And New Mechanism Data Bode Well” - Scrip, 13 Nov, 2017.)

Opdivo has historically held the lead in the IO market, and brought in $4.9bn across all indications in 2017. But times seem to already be changing. In the fourth quarter, Keytruda drew almost level with just under $1.3bn, compared to $1.36bn for Opdivo. Keytruda’s full year 2017 sales were $3.8bn. As of the firm’s Feb. 2 earnings call, in the US roughly 55% of Keytruda sales came from lung cancer, with about 15% from melanoma and 5% each from bladder and head and neck cancers. (Also see “Buoyed By US Tax Reform, Merck Plans $12bn In Capital Investments” - Scrip, 2 Feb, 2018.)
Since the Company was founded 34 years ago, Masters has been dedicated to ensuring that patients around the world have access to important, and, often life-saving, medicines, that they need.

As an internationally recognised pharmaceutical company with extensive global reach, Masters continues to focus on servicing the needs of patients in emerging markets, delivering unavailable medicinal products, often to remote areas, where careful planning is required to ensure the safe handling of the medicines including robust pharmacovigilance and logistical systems are in place.

Governed according to UK and USA laws, Masters is familiar with the challenges of operating across differing legal and ethical frameworks in order to accommodate the varied needs of our customers, and to expand the range of medicines available to health care professionals and their patients.

A primary business activity for Masters is the sourcing of superior innovative medicines, and over the last three decades the Company’s infrastructure has developed to support this crucial work. Masters two divisions, Masters Speciality Access (MSA), and, Masters Speciality Medicines (MSM) operate in synergy. MSA supplies unlicensed medicines into emerging markets, and, MSM partners with life science companies to register medicines under Masters name; guaranteeing a reliable and affordable source of medicines for the future. Together, the two divisions help Masters to achieve its vision of “Medicines Reaching Further”, and to meet the needs of patients in various regions of the world, including, South and Central America, Middle East, and the Caribbean.

In addition to its UK headquarters, Masters has subsidiaries in Brazil, Colombia, Uruguay, El Salvador, USA, and UAE, actively supporting Masters activities in these regions, helping to deliver the high quality service our customers expect, and, improving access to medicines in a range of therapeutic areas, including, oncology, haematology, orphan diseases and pain management.

A further extension of our existing commitment are the plans that Masters has to expand its horizons in 2019, registering more branded products and facilitating the local availability of the registered products of our partners. As Masters continues its growth and expansion plans, maintaining strong relationships with our existing and new partners remains a priority for us.

Masters is the go to company for the distribution of niche, specialist and difficult to handle medicines, managing their supply diligently and delivering them in to territories where Masters has many years of unrivalled expertise.
AbbVie Hit Harder By EU Humira Biosimilars Than Projected

By Joseph Haas

The event AbbVie Inc. has planned for and investors have obsessed about since the Chicago-area firm’s spinout from Abbott Laboratories Inc. in 2014 has finally begun, and biosimilar competition to Humira (adalimumab) in Europe is having a bigger initial impact than the pharma projected.

Four sponsors launched adalimumab biosimilars simultaneously in Europe in mid-October. Chairman and CEO Rick Gonzalez said during AbbVie’s third quarter earnings call Nov. 2 that discounting, which occurs on a market-by-market basis in the EU, has been greater than expected, ranging from 10% to 80% depending on the country. The pharma now anticipates 26%-27% ex-US sales erosion for its top-seller, compared to prior expectations of 18%-20% erosion in 2019, the first full year of adalimumab biosimilars.

HCV competitor Gilead Sciences Inc. announced in September that it would spin out an affiliate next year to market authorized generics of its HCV drugs – Harvoni (sofosbuvir/ledipasvir) and Epclusa (sofosbuvir/velpatasvir) – in an effort to win market share back from AbbVie. (Also see “Gilead’s HCV Authorized Generics Effort Will Draw Market Share From AbbVie” - Scrip, 24 Sep, 2018.)

In other therapeutic areas, Gonzalez pointed to AbbVie’s oncology franchise as a source of continuing growth past the Humira patent cliff. “Today, our hematological oncology portfolio is now annualizing above $4bn and growing at a robust rate, including growth of more than 48% in the third quarter,” he told the call. “As we continue to generate data that validates the utility of both Imbruvica and Venclexta across a wide range of patient populations and cancer types, we expect this franchise to drive significant growth for many years to come.”

The oncology drugs did better than expected – nine points above consensus. Imbruvica (ibrutinib) posted global sales of $972m, good for 41.3% year-over-year growth, including $812m in domestic sales. Venclexta (venetoclax) continues its growth trajectory as well, with its $96m – $69m US/$27m ex-US – comprising better than 100% growth across the board compared to third quarter 2017.

Humira Biosimilar Discounts Steeper Than AbbVie Expected

Good news elsewhere did not deter analysts from the topic of Humira biosimilar impact, now that the initial copies have reached the market in Europe. AbbVie has reached multiple settlements with generic drug makers that stave off US biosimilar competition until late 2023, and the for AbbVie a year earlier, almost entirely on the strength of two-drug combo Mavyret (glecaprevir/pibrentasvir). (Also see “AbbVie HCV Revenue Surprises Again, But Falloff Is Coming” - Scrip, 27 Jul, 2018.) Gonzalez noted that Mavyret gives AbbVie approximately 50% market share in HCV globally at present. Mavyret totaled $839m in worldwide sales from July through September, with $444m in the US and $395 ex-US.

Hepatitis C drug sales of $862m were down sequentially from $973m in the second quarter, but still substantially higher than the $276m the HCV franchise was bringing in for AbbVie a year earlier, almost entirely on the strength of two-drug combo Mavyret (glecaprevir/pibrentasvir). (Also see “AbbVie HCV Revenue Surprises Again, But Falloff Is Coming” - Scrip, 27 Jul, 2018.) Gonzalez noted that Mavyret gives AbbVie approximately 50% market share in HCV globally at present. Mavyret totaled $839m in worldwide sales from July through September, with $444m in the US and $395 ex-US.
company continues to guide for continued overall growth for the autoimmune powerhouse. (Also see “Sandoz And AbbVie Biosimilar Humira Settlement: What Does It Mean?” - Scrip, 12 Oct, 2018.)

The first query during the call’s Q&A portion brought up the topic of the EU launches of adalimumab biosimilars by Amgen Inc., Sandoz International GMBH, Samsung Bioepis Co. Ltd. and Mylan NV. Clearly prepared for the topic, Gonzalez launched into a lengthy and detailed answer. The launches only occurred about two weeks ago, he noted, but that still has given AbbVie a view on pricing of the products in virtually every EU market.

With discounts ranging from 10% to 80%, AbbVie has seen the highest discounts in the Nordic countries “where it’s winner-take-all,” Gonzalez said.

“The discounting has been on the higher end of the planning scenarios that we have laid out, and still within the planning scenarios that we have laid out, but a little bit on the higher end of that,” he began, adding that the discounts are also at the higher end of what was seen for biosimilars of Johnson & Johnson’s Remicade (infliximab) and Amgen’s Enbrel (etanercept), which AbbVie saw as indicators for what to expect with Humira.

With discounts ranging from 10% to 80%, AbbVie has seen the highest discounts in the Nordic countries “where it’s winner-take-all,” Gonzalez said. Similar trends were seen in the Nordic region for biosimilar infliximab and etanercept, he added. What occurred in the Nordic markets was not a surprise, the exec continued, and “not a big part of our business” – accounting for about 4%-5% of international Humira revenues.

AbbVie announced it had agreed upon its first tender Nov. 1, accepting an 80% discount but not specifying the country of the agreement. (Also see “AbbVie Defends Humira With Aggressive Discount In First EU Tender “ - Scrip, 1 Nov, 2018.) Based on Gonzalez’s commentary, it seems likely that tender was made in one of the Nordic markets.

Overall outside the US, about two-thirds of Humira revenue will come from what Gonzalez calls “blocked” markets – those in which the branded product and biosimilars compete at the same tendered price. France is an example of a market where AbbVie now will compete with adalimumab biosimilars at identical pricing.

The other one-third of markets where biosimilars of Humira are registered are still being negotiated, he said. “We have pricing in those markets,” Gonzalez said. “We have a pretty good idea of where we stand, but there’s still an opportunity for some movement in those markets.” He noted AbbVie will need “probably another month or two for that to be able to play out and for us to have a firm understanding of where the discounting will settle out and where our volumes will settle out.”

AbbVie now estimates that biosimilar erosion in 2018-2019 will be higher than it estimated previously, at 26%-27% rather than 18%-20%, the exec said. But the company expects this discounting to moderate after 2019 – an assertion that multiple market analysts disagreed with in same-day notes.

BMO Capital Markets analyst Alex Arfaei said he has long expected that a moderating trend of erosion in Europe was unlikely due to multiple factors. “We continue to disagree with AbbVie’s updated commentary because we doubt Humira’s ex-US erosion will moderate after 2019, because we expect [an] increased number of biosimilar entrants in current and new geographies, availability of interchangeable biosimilars by roughly 2021-2022, and more aggressive adoption of biosimilars in Europe per recent trends,” he wrote Nov. 2.

Leerink Partners analyst Geoffrey Porges also diverged from Gonzalez’s prediction, saying “we do not have evidence from prior EU biosimilar launch dynamics that the pace of discounting will slow in the second year of availability of biosimilars, and with multiple entrants and a still substantial revenue base (about $4.5bn) we would expect erosion to intensify in 2020, not slow.”

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Roche’s Ocrevus: A Rare First-Year Blockbuster

By Jessica Merrill

Roche’s multiple sclerosis drug Ocrevus (ocrelizumab) appears to have set a new bar for commercial drug launch success among recent launches (excluding drugs for hepatitis C). Ocrevus generated $935m (CHF869m) in sales in 2017 in just nine months after launching in the US in April, nearly reaching blockbuster status in under a year on the market.

Drugs that reach $1bn in sales that fast don’t come around every year. Ocrevus has outpaced other notable launches in the last six years, including Pfizer Inc.’s Ibrance (palbociclib), Novartis AG’s Cosentyx (secukinumab), Bristol-Myers Squibb Co.’s Opdivo (nivolumab), Biogen’s Tecfidera (dimethyl fumarate), Johnson & Johnson/Bayer AG’s Xarelto (rivaroxaban) and Regeneron Pharmaceuticals Inc.’s Eylea (aflibercept).

One launch that does stand out is GlaxoSmithKline PLC’s HIV drug Tivicay (dolutegravir), which together with a combination pill Triumeq (abacavir/dolutegravir/lamivudine) generated $1.85bn (£1.3bn) in a full 12 months on the market in 2015, after launching late in 2014, not an easy direct comparison.

Even when it comes to one of the best-selling drugs of all time, Pfizer’s Lipitor (atorvastatin), Ocrevus surpassed the bar, though just barely.

Even $200m in launch-year sales is generally considered a commercial success, a signpost that a drug is on a track toward eventual blockbuster status.

Ocrevus is a key drug for Roche as it looks to move forward into an era that will include biosimilar competition to many
of its longstanding blockbusters, including Herceptin (trastuzumab), Avastin (bevacizumab) and Rituxan (rituximab).

Ocrevus was approved by FDA in March as the first drug for an underserved patient population, primary progressive MS (PPMS) patients, as well as for relapsing-remitting MS (RRMS). The strong efficacy data supporting the approval and competitive pricing have likely powered the launch. Roche priced Ocrevus at a 20% discount to other MS therapies on average, including the standard interferons. (Also see “Roche Set For Disruptive Entry To MS Market With ‘Brave’ Ocrevus Pricing Strategy” - Scrip, 29 Mar, 2017.) Ocrevus was only recently approved in Europe. (Also see “All Systems Go as Roche MS Drug Ocrevus Secures EU Okay At Last” - Scrip, 12 Jan, 2018.)

The drug was an early standout among the 2017 class of drugs. (Also see “A Year To Remember For US Drug Launches” - Scrip, 29 Dec, 2017.) But Roche’s year-end financials, reported Feb. 1, revealed the drug has surpassed other big launches in the last five years based on revenues. Hepatitis C drugs were excluded because of their unusual launch trajectory involving a fast initial uptake that slowly recedes as patients are treated, and some HIV drugs also had stronger early sales. Gilead Sciences Inc.’s Sovaldi (sofosbuvir) is well recognized as the most notable launch of all time after it generated $10.28bn in 2014 following its launch in December 2013. (Also see “Head Of The Class: A Star Stands Out Among 2014 Drug Launches” - Pink Sheet, 5 Jan, 2015.)

Among more traditional launches in the last six years, Ocrevus’ revenues have outpaced industry’s fastest success stories. Multiple sclerosis is clearly a strong therapeutic category to launch into. Biogen’s oral multiple sclerosis pill Tecfidera generated the next highest revenues in the same time period; Tecfidera generated $876m in 2013 after launching in April of that year. (Also see “Tecfidera Stands Out From The Pack Of 2013 Drug Launches” - Pink Sheet, 13 Jan, 2014.)

Bristol’s immuno-oncology blockbuster Opdivo generated $942m in 2015, but that was after a full year on the market as it was approved by FDA in December 2014. Regeneron’s Eylea likewise is remembered among the best new launches, but generated $838m in 2012, a full year after launching in late 2011. J&J/Bayer’s blood thinner Xarelto (rivaroxaban) brought in $864m in a full year in 2013 after launching in the second half of 2012.

Pfizer’s first-in-class CDK-4/6 inhibitor Ibrance yielded $723m in 2015 after launching in February. Novartis’ Censentyx, revered as a recent commercial success that generated $2.1bn in 2017, only generated $261m in 2015 following its launch that February.

Going back even further into the drug archives, even when it comes to one of the best-selling drugs of all time – Pfizer’s Lipitor (atorvastatin) – Ocrevus surpassed the bar, though just barely. Lipitor generated $865m in sales in 1997 under the ownership of Warner Lambert after launching in February of that year.

Bristol’s Plavix (clopidogrel) brought in $547m in its first full year on the market in 1999 and Merck’s Januvia generated $667.5m in 2007, its first full year on the market.

With that historical context in mind, it’s pretty clear Roche has a winner on its hands.

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We are grateful for our partners at BMS. Our team looks forward to continuing to work with both new and current partners to use rHuPH20 to deliver their treatments subcutaneously.
Narasimhan: Novartis’ Specialized Portfolio Will Lead To Bigger Breakthroughs And Greater Value

By Alex Shimmings

When Vas Narasimhan stepped into the CEO shoes in February he set out a strategy to focus Novartis AG as a leader in transformational medicines by investing in differential technologies that will enable it to outgrow its competitors. During the company’s first R&D day since the previous R&D chief took over at the top, in London on Nov. 5, he talked to journalists about the progress made towards a specialized portfolio on the back of three innovative technologies, and the challenges involved.

Novartis has made swift and decisive moves already in executing this strategy, with decisions to quit consumer healthcare with a sale to GlaxoSmithKline PLC of its stake in their Consumer Healthcare Joint Venture, to spin off Alcon Inc. (Also see “Novartis Sees The Light And Plumps For Alcon Spin-Off “ - Scrip, 29 Jun, 2018.), and to sell some of its Sandoz US generics business to Aurobindo Pharma Ltd. (Also see “Big Statement By Aurobindo As It Seals $1bn Sandoz US Deal “ - Scrip, 6 Sep, 2018.). This came in tandem with two acquisitions designed to bring in novel technology platforms and deepen its innovative medicines portfolio. It announced a $2.1bn purchase of radiopharmaceutical company Endocyte Inc. last month, building on last year’s $3.9bn acquisition of Advanced Accelerator Applications SA (AAA), and in April spent $8.7bn on gene therapy company AveXis Inc. to get its hands on a promising gene therapy technology plus a lead candidate, AVXS-101, a potential cure for infants with type 1 spinal muscular atrophy (SMA). (Also see “Novartis Tunes Into Radiopharmaceuticals With Endocyte Buy” - Scrip, 18 Oct, 2018.) (Also see “Novartis Goes Big On Gene Therapy With $8.7bn AveXis Acquisition” - Scrip, 9 Apr, 2018.)

Together with its established cell therapy platform that produced Kymriah, Narasimhan said, the gene therapy and radioligand technologies these acquisitions brought form the three “platforms for innovation that I believe on top of small molecules and biologicals will be enable us to get to new medicines that will have significant impact and hopefully also drive our financial performance and growth.”

Narasimhan said the deals were just a start. “We have been building in-house capabilities in these three areas but I do have a belief that we need to continue to do bolt-on acquisitions in our innovative meds core,” he told Scrip. “Historically, when we were a much more diversified company our capital needed to be spread out across many different businesses, we needed to do acquisitions in generics, or animal health or consumer health, and now with this new focus we can go deeper into these new areas where we want to build leadership but also in invest in. I believe that over the long term, if we do that consistently and make bolt-on acquisitions and deals to complement our internal capabilities, we will build a much more valuable company over time.”

Narasimhan said the stakes were high but the investments justified. “There are higher risks as you continue to focus on small molecules and biologics. I think there is a risk in not pushing into new technologies and new areas of science to find breakthrough medicines. I think in the end society will always reimburse and pay if we find these...”

“Getting out ahead leads to a difficulty for others to follow”  
– Vas Narasimhan, Novartis CEO
breakthrough medicines and that’s going to require us to move beyond our previous playing fields. I want us to be a company that is willing to make the bets to go there. We may not always get it right but I think that gives us a better chance to be a leading, high technology innovative medicines company.”

Getting in early is key to fending off rivals, he says. “My bet in these three platform areas is getting out ahead leads to a difficulty for others to follow.” With CAR-T therapy Kymriah, for example, Novartis has already forged strong links with treatment centers around the world, and has built a fully scaled and licensed manufacturing network. “Our ability then to be the logical partner of choice for smaller companies with new technologies as well as to use our own discoveries gives us a big advantage because anyone else building from scratch is basically Novartis in 2015 – we have a four-year head start on them.” This is no different with the radioligand technology, he added, given the supply chain logistics in handling radioactive material, which must be received by the patient before it degrades. “All the intricacies involved in that again gives us a head start.”

Gene therapy will differ in that it is a much more competitive arena. “Our bet there is around the manufacturing platform and we will have scaled facility in Chicago and North Carolina, and so I think that will give an advantage. Now we have to be mindful of the next disruption, for example in cell therapy – is someone going to come up with a much shorter manufacturing process? If so, we want to be that company or partner with the company that does. Will someone solve allocart – the idea that you have off-the-shelf CAR-T? We haven’t seen it yet but we definitely have to be ready for it... Again we have built up this huge expertise in house so we believe we can assess these technologies the best.”

The AAA and AveXis deals both had the added advantage of bringing with them a late-stage asset along with the technology (Lutathera and AVXS-101, respectively). “We got the best of both worlds. We got a platform and we got a near-term launch. That would be my preferred solution wherever possible looking externally, but I would say that we are not afraid to make [earlier] investments,” he added, citing the partnership with antibody technology company, Xencor Inc. (Also see “Novartis Deal Gives Xencor $150m Up Front, Up To $2.41bn In Milestone Fees” - Scrip, 28 Jun, 2016.)

The two purchased companies are being maintained as distinct entities within Novartis, and cell therapy has also been carved out as a separate unit. That way they can each leverage Novartis resources while they build out their technologies and move towards the market with all the ensuing pricing and reimbursement difficulties. This means they can “work through all of those things that we don’t have to deal with when we are dealing with Entres-то,” Narasimhan said. “It’s a business model transformation when you think about it.”

In terms of pricing, he said, the transformational nature of the novel treatments should speak for itself. “I think the science is pretty compelling. We are in a situation where we can cure children with pediatric ALL of cancer and with AVXS-101 we arguably have the possibility to cure children from deadly rare muscular diseases,” he said. “The issue here is actually a budgetary problem –it’s all at once as opposed to 10-20 years and while we are fully prepared to accept payment over time, the system’s not ready.”

For potential breakthroughs like AVXS-101, which has already been filed in the US, EU and Japan, he said Novartis would price well below the cost effective pricing thresholds, even though in this case it maintains that this could be as high as $4-5m a treatment. The company has started to engage with payers over possible payment structures. “I do believe over time we will get to the place when enough of these gene therapies come the system will be able to pay us over time. Over 10 years becomes a lot less of an issue because you will be spreading this out and if there is a reversion we can think about outcomes based pricing etc. But right now that’s the challenge we are in because the payment happens on one day even though we are giving a lifetime of benefit. As opposed to a chronic therapy that would give you a worse outcome for the child. More expensive system but sounds nicer from a budgetary smoothing standpoint.”

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Just over two years into its five-year effort to fundamentally transform its R&D activities, Takeda Pharmaceutical Co. Ltd. says the initiative has led to a more focused approach and an enlarged pipeline, fueled by an open approach to partnering.

With a global emphasis on oncology, gastroenterology, neuroscience and vaccines, the company’s drug discovery units have been halved over the past few years to three - in Boston (US), Shonan (Japan), and San Diego (US).

Fixed costs have been reduced through this and other restructuring, freeing up resources for partnering and acquiring or generating innovation, and investing in building and progressing the pipeline, president and CEO Christophe Weber told the company’s recent R&D Investor Day in Tokyo.

A major step was taken last year to spin out the company’s in-house drug discovery research division into a new entity, Axcelead, which became an independent company earlier this year with support from other investment partners. (Also see “What A Whiz! Takeda Spins Off Discovery Op Axcelead Into New Fund” - Scrip, 6 Aug, 2018.)

Meanwhile, times to select development candidates have been cut, and “We are on track to achieve 11 planned candidate selections in fiscal 2018 [ending next March 31], of which five are small molecules,” Chief Medical and Scientific Officer Dr Andrew Plump told the meeting.

In total, 30 pipeline assets have progressed since April 2016, 45% of the current pipeline is partnered, and 38% of the pipeline has orphan drug designation.

The R&D transformation process began in 2015, and the main strategic takeaway messages were that changes have been made to the previous “top-down hierarchical organi-
zation” to create a more performance- and outcomes-driven culture to push innovation, promote experimentation and tolerate and learn from failure, Plump said.

What Will Shire Bring?

With the planned $62.4bn acquisition of Shire still on track to close in the calendar first half of 2019, another key message from the event was that there would be no fundamental change in R&D strategy in the merged company.

Antitrust regulatory clearances around the deal have so far in major markets such as the US and China have been “seamless”, Plump noted.

“The Shire acquisition is not disruptive to our R&D...we have already done the disruption”
– Takeda CEO Christophe Weber

While the deal will bring further financial stability and enable current R&D investment to be raised by at least $1bn - a 33% increase from the current base - Plump said the main change would be the added capability around rare diseases.

Weber reiterated a similar message on the sort of R&D expertise Shire will bring, without derailing overall strategy. “In that sense, the Shire acquisition is not disruptive to our R&D, which in our mind was very important because you often pay a heavy price with M&A on the R&D front because you have years of disruption.

“This will not be the case here because we have already done the ‘disruption’ if you like.”

New Rare Diseases Unit

Christopher Morabito, who is heading up the R&D integration process for Takeda, told the meeting that bringing together the pipeline assets would be helped by the creation of a new specific rare diseases therapeutic area unit.

This is expected to focus on “probably on a few specific indications such as hereditary angioedema, hematology including hemophilia, and lysosomal storage diseases,” reflecting Shire’s current portfolio and pipeline in these indications.

This greater focus on rare diseases is also expected to help further tighten up the development cost base given the smaller patient populations, which will provide the chance “to be more productive with less financial investment,” Morabito predicted.

More widely, synergies in the acquisition will “focus on pipeline rationalization, looking for redundancies in the workforce, increasing the leanness by tightening up that infrastructure, and then ultimately thinking about how to better leverage the R&D rare diseases expertise in order to be more effective,” Morabito added.

Besides the specific R&D assets Shire will bring, “Shire also has this strong capability of working with patients directly, working with patients' organizations, working with families” to get new medicines to patients in an effective way, he added.

Morabito also pointed to Shire’s “world-class regulatory expertise and top-notch talent...for clinical trial execution - it’s a machine”. The company works well both internally and with partners, and for instance enrolled the Takhzyro (lanadelumab-flyo) Phase III trial for hereditary angioedema - a “very rare disease” - at record pace.

“So we look forward to learning from them about how to be even more effective operationally, in particular with clinical trials,” he said.

Addressing a question on how the corporate cultures might mesh, Morabito said the reception in Shire to “Takeda-ism”, a value system that includes integrity, fairness, honesty, has been “incredibly positive”.

Continued Partnering To Build Out Pipeline

Despite the pipeline additions that Shire and other acquisitions have brought, Plump conceded at the meeting that “our Phase III pipeline today is not where it needs to be.”

In future, more spending will go towards the innovative pipeline, rather than the 60% currently spend on life cycle management, although this figure in part reflects multiple indications being pursued for single or combination products in the oncology space.

Continued partnering, through in-licensing or targeted
acquisitions, will remain a key facet of R&D strategy and a core part of Takeda’s overall R&D model, Plump stressed, helped by a dedicated, US-based Center for External Innovation.

The rationale here is that this will enable the company to access external innovation while keeping in-house activities focused, and the same principles will be applied to Shire assets, Morabito noted.

Takeda entered into 56 partnerships in the fiscal year ended last March 31, linked to its core therapeutic interests or technology platforms.

However, given the size and financing needs of the Shire deal, and the already stated goal to pay off related debt in three to five years, Plump explained that: “it’s unlikely that we’ll have the resources to make a substantive acquisition”.

Nevertheless, the expectation is that, within a “reasonable time frame, we’ll have a cash reserve to go out and do more through acquisition or licensing.”

Meanwhile, Takeda’s iPark open innovation initiative at its Shonan site in Japan is aiming to foster ventures and collaborations with industry, academia and government, although Weber explained that the company does not have any binding commitment or first refusal rights to projects developed by tenants.

Near Term Highlights
Turning to specific current Takeda pipeline assets, Plump highlighted three “next generation” therapies that the company believes will provide transformative benefits for patients, and for which pivotal results are expected in the near term.

These are: the NAE/NEPD8 inhibitor pevonedistat, in Phase III for high-risk myelodysplastic syndrome; the EGFR/HER2 inhibitor TAK-788 for non-small cell lung cancer (Phase I); and the dengue vaccine TAK-003, for which the Phase III primary endpoint readout will be one of the “BIVIs” (big important value inflections) this fiscal year.

Results for the live, attenuated tetravalent dengue vaccine are expected by the calendar end of this year, and the company is confident on both the efficacy and safety fronts. (Also see “Takeda’s Dengue Vaccine Candidate Aims To Avoid Dengvaxia Problems” - Pink Sheet, 21 Dec, 2017.)

‘Amazing’ China
While Takeda had been lagging in progressing its key innovative products in China, a ring-fenced budget had been provided to get it up to development speed in the country, Plump said.

This is expected to lead to the launch of six new products and 14 new indications there by 2020, including Entyvio (vedolizumab) for inflammatory bowel disease, for which a global data package has been allowed to support the NDA and priority review.

“All of Takeda’s global programs now include China from the early development phase [to enable parallel development] - it’s just so much opportunity that we’re beginning to realize in China. What’s going on in China right now is absolutely amazing,” Plump commented.

“The speed with which China is embracing innovation is just remarkable.”

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Immuno-Oncology’s Next Wave: Key Targets And Emerging Players

By Mandy Jackson

While there are plenty of drug makers that aren’t developing cancer treatments, there’s no denying that immuno-oncology (IO) is the hottest ticket in biopharma today based on the ever-increasing number of novel IO targets, the growing pipeline of immunotherapies in development, and the volume of dealmaking in the space.

The companies who’ve been first to market with programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) checkpoint inhibitors are leading the way forward in immuno-oncology: Bristol-Myers Squibb Co. with Opdivo (nivolumab), Merck & Co. Inc. with Keytruda (pembrolizumab) and, just recently, Roche’s Genentech Inc. subsidiary with Tecentriq (atezolizumab). Following close on their heels with Phase III compounds are AstraZeneca PLC with durvalumab and avelumab from partners Pfizer Inc. and Merck KGAA. (Also see “Early Tecentriq OK Gives Roche/Genentech Jump On PD-L1 Bladder Cancer Market” - Scrip, 18 May, 2016.)

Bristol-Myers is likely to maintain its commercial lead, and possibly it’s lead in the clinic, since Merck’s Keytruda revenue lags Opdivo, which got the early lead in the lucrative lung cancer market. And, unlike Keytruda, Opdivo’s label doesn’t require lung cancer patients’ tumor samples to be screened for PD-L1 expression levels. (Also see “Bristol Getting Eagerly Awaited First-Line Opdivo Lung Data Earlier Than Expected” - Scrip, 28 Apr, 2016.) Bristol’s immuno-oncology edge in sales and clinical programs is boosted by the firm’s first approved checkpoint inhibitor, the cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor Yervoy (ipilimumab), for patients with unresectable or metastatic melanoma. Bristol then nabbed the first combination approval, for Opdivo and Yervoy in melanoma, and is leveraging both as the base for IO combinations.

Ten Key Targets, Most Drugs Preclinical
But PD-1/PD-L1 and CTLA-4 are just the beginning for immuno-oncology as the field expands to other mechanisms and from single-agent therapies to therapeutic combinations that not only take the brakes off of the immune system, but also shift it into overdrive for an even more aggressive attack against tumor cells.

Scrip looked at 10 different immuno-oncology targets for the purposes of this report and spoke with some companies that are focused on novel immunotherapies based on these other targets. The field is so new, however, that most programs still are in early stages of development.

Of 10 targets with 99 different immunotherapies in development, only five have been approved, 39 are in the clinic and 55 are preclinical, according to Pharma Intelligence’s Biomedtracker database.

Of 10 targets with 99 different immunotherapies in development, only five have been approved, 39 are in the clinic and 55 are preclinical, according to Pharma Intelligence’s Biomedtracker database. Those 10 targets are: PD-1/PD-L1, CTLA-4, granulocyte-macrophage CSF or its receptor (GM-CSF/GM-CSFR), lymphocyte-activation gene 3 (LAG3), T-cell immunoglobulin and mucin domain 3 (TIM3), toll-like receptor (TLR) family, indoleamine 2,3-dioxygenase (IDO), cluster of differentiation 47 (CD47), CD40 and OX40 (CD134). (Also see “Scrip’s Rough Guide to Immuno-Oncology” - Scrip, 1 Jun, 2015.)

These targets generally are addressed by monoclonal antibodies, small molecule drugs and therapeutic vaccines, but cell therapies also are an important modality for the immuno-oncology field. Two out of the top 10 therapies to watch in Scrip’s preview of the American Society of Clinical Oncology (ASCO) annual meeting from June 3 to 7 in Chicago are chimeric antigen receptor T-cell (CAR-T) therapies from Juno Therapeutics Inc. and Novartis AG. (Also see “Ten Programs To Watch Out For At ASCO” - Scrip, 20 May, 2016.)
However, there are no approved CAR-T therapies. The five FDA-approved immuno-oncology agents include four monoclonal antibodies and one oncolytic viral therapy – Amgen Inc.’s Imlygic (talimogene laherparepvec), which produces the immuno-stimulatory protein GM-CSF and is indicated for local treatment of unresectable melanoma lesions that recur after surgery. (Also see “Amgen’s Imlygic 1st FDA-Approved Oncolytic Virus Therapy” - Scrip, 28 Oct, 2015.)

The PD-1/PD-L1 inhibitors, Yervoy, Imlygic and the forthcoming CAR-T therapies were preceded by Dendreon Corp.’s Provenge (sipuleucel-T), an autologous cellular immunotherapy. However, the prostate cancer treatment generally has been a commercial failure with Dendreon filing for bankruptcy to pay its debts and selling Provenge and related assets to Valeant Pharmaceuticals International Inc. in 2015. (Also see “Valeant ups bid for Dendreon’s Provenge to $400m” - Scrip, 6 Feb, 2015.)

Early-Stage Doesn’t Reduce Excitement

Among the 10 targets Scrip reviewed recently, only 40% of the therapeutic candidates in the pipeline are being studied in humans and only four therapies are in Phase III clinical trials. Another five are in Phase II, seven are in Phase I/II and 23 are in Phase I trials. Yet the early stage of development in these targets hasn’t reduced the interest in them.

In fact, Genentech probably wouldn’t present its Phase I data for the OX40 inhibitor RG7888 (MOXR0916) at ASCO, given the monoclonal antibody’s early development stage. But there is so much interest in immuno-oncology, especially in relation to new targets, that the company decided to share its OX40 data at the annual cancer treatment meeting, Genentech VP-BioOncology and Exploratory Clinical Development Stuart Lutzker told Scrip. The company also wanted to share noteworthy efficacy that’s been observed even in early dose escalation results.

In a June 4 presentation at ASCO, data will show objective response rates among 44 patients treated with RG7888 plus the company’s newly approved PD-L1 inhibitor Tecentriq in seven different dose cohorts (n=25) and a serial biopsy cohort (n=19) during the Phase I dose escalation portion of an ongoing clinical trial. The abstract indicates that the combination was well tolerated with no treatment-related adverse events leading to study discontinuation. Efficacy data will be presented at the meeting.

Lutzker noted that patients with sarcoma – a group that hasn’t been well-served by anti-PD-1 monotherapy – and renal cell carcinoma were among the Phase I study’s participants, which included five people previously treated with a PD-1 inhibitor. Some of the renal cell carcinoma patients had confirmed partial responses and some patients experienced tumor shrinkage.

“We think that mechanistically [RG7888] will work best in a combination,” Lutzker said. “Atezolizumab as a single agent provides benefit to patients, but we think the benefit could be enhanced by an agonist antibody that increases the pool of effector immune cells where atezolizumab takes the brakes off the immune system. We think that’s a very exciting combination.”

Biomedtracker analysts were optimistic about RG7888 in a mid-May report issued after ASCO released abstracts for its annual meeting. “The observation of objective responses here is promising, particularly if the five patients who had previously received PD-1/PD-L1 antibody therapy showed enhanced responses,” the report notes.

Combinations To Follow In PD-1 Footsteps

Regeneron Pharmaceuticals Inc. also has a PD-1 inhibitor in the clinic – the mid-stage biologic REGN2810 – that it’s developing as a backbone for immunotherapy combina-
Combinations can improve the impressive efficacy seen with PD-1 inhibitor monotherapy and the right combinations will do so with manageable side effects.”

– George Yancopoulos

There are few companies that have made a long-term, deep commitment in this area, years ago, to come up with a lot of different potential agents to bring to bear on this problem,” Yancopoulos said.

Preclinical programs in Regeneron’s immuno-oncology portfolio include therapies that target LAG3 and glucocorticoid-induced tumor-necrosis-factor-receptor-related protein (GITR). The company also has a Phase I bispecific antibody called REGN1979 that targets CD20 on B cells and CD3 receptors on T-cells.

Regeneron and Sanofi agreed to expand their long-term relationship in July with a new collaboration worth more than $2bn to Regeneron, including a $640m upfront fee, to co-develop immuno-oncology therapies. The deal included REGN2810, which is in Phase II for the treatment of advanced cutaneous squamous cell carcinoma – a study that could support US FDA approval. (Also see “Sanofi plays catch-up in immuno-oncology with new Regeneron deal” - Scrip, 28 Jul, 2015.)

In Phase I data for REGN8210 that will be presented at ASCO on June 5, the disease control rate was 62.8% in patients with solid tumors, including 27 out of 43 clinical trial participants who achieved complete responses, confirmed and unconfirmed partial responses, or stable disease.

Less Competition, But A Lot Of Interest

Incyte Corp. has one of the hottest properties in immuno-oncology, an IDO inhibitor called epacadostat that is or will be tested in combination with all three of the approved PD-1/PD-L1 inhibitors as well as AstraZeneca’s PD-L1 inhibitor durvalumab. There are just eight IDO-targeting therapies in the development pipeline with only three in the clinic, although two of the clinical drug candidates are in Phase II, including epacadostat.

Scrip also interviewed Incyte Chairman, President and CEO Herve Hoppenot about his company’s immuno-oncology pipeline during the J.P. Morgan Conference in January, and Hoppenot claimed that Wilmington, Delaware-based Incyte began developing its IDO inhibitor before anyone else was interested in the target. Now, the company has clinical collaborations with multiple big pharma players to test its drug in combination with their PD-1/PD-L1 inhibitors. (Also see “Merck, AZ, Roche, BMS work off grid for mix-and-match immuno-oncology” - Scrip, 12 Jun, 2015.)

Incyte and Merck announced a pivotal Phase III clinical trial in October to test Keytruda plus epacadostat as a first-line treatment for advanced metastatic melanoma. Other epacadostat trials include a Phase I/II study with Keytruda and another in combination with Opdivo in certain advanced solid tumors and lymphomas; a Phase I study with Tecentriq for previously treated metastatic non-small cell lung cancer (NSCLC); and a Phase I/II study in combination with durvalumab for certain advanced solid tumors. (Also see “Incyte and Merck Push I/O Drug Forward” - Scrip, 13 Oct, 2015.)

And like Regeneron, Incyte also is developing its own PD-1 inhibitor – an asset licensed from Jiangsu Hengrui Medicine Co. Ltd. in September – which it will market in combination with its other immuno-oncology drugs. The Hengrui deal was about “adding optionality to our portfolio for the long term,” Hoppenot said. (Also see “Incyte, Hengrui In ‘Biggest Ever’ China Pharma Out-Licensing Deal” - Scrip, 4 Sep, 2015.)

“We have to prove that a PD-1 inhibitor plus an IDO drug is better than PD-1 plus CLTA-4,” he said.
Forget Boosting Anti-PD-1 Therapies; Can A PD-1 Inhibitor Boost Novel Agents?

PD-1 inhibition may be just the savior that Berkeley, California-based Aduro Biotech Inc. needs to rescue its lead development program. Aduro had a setback recently with two of its lead therapeutic candidates in the Phase IIb ECLIPSE clinical trial testing its immunotherapies CRS-207 and GVAX Pancreas in patients with advanced pancreatic cancer.

Median overall survival for patients with metastatic pancreatic cancer, who failed at least two prior therapeutic regimens and were treated with the company’s combination of CRS-207 and GVAX Pancreas, was 3.8 months – significantly lower than the 5.4 months of survival achieved by patients treated with CRS-207 alone and 4.6 months for individuals who received chemotherapy. (Also see “Stockwatch: Fireworks Or Ballistic Missiles In Biotechnology?” - Scrip, 23 May, 2016.)

CRS-207 is a product of Aduro’s live, attenuated, double-deleted Listeria monocytogenes (LADD) technology. It uses the listeria virus to deliver mesothelin to provoke an immune system attack against tumor cells expressing that antigen. GVAX Pancreas is a cell-based cancer vaccine that is designed to induce an immune response against multiple pathogens, including GM-CSF.

Aduro Chairman, President and CEO Stephen Isaacs noted during a conference call after the ECLIPSE results were revealed on May 16 that late-stage, metastatic pancreatic cancer is very difficult to treat, but he said the company still was “surprised” that the Phase IIb results diverged from Phase IIa data for Aduro’s combination regimen. (Also see “Aduro shows survival benefit with pancreatic cancer vaccine duo” - Scrip, 16 Jan, 2014.)

While the company will no longer pursue CRS-207 plus GVAX for heavily pre-treated pancreatic cancer patients, Aduro remains hopeful for success in the ongoing Phase II STELLAR trial, which is testing CRS-207 and GVAX in combination with Opdivo versus CRS-207 and GVAX alone in metastatic pancreatic cancer patients who’ve gone through one prior round of chemotherapy.

William Blair analyst John Sonnier said in a May 16 research note that Aduro’s LADD platform is likely to perform well when used in combination with other immunotherapies, because it “has continually shown the ability to stimulate an immune response to the target antigen while also exhibiting a favorable safety profile.”

There are higher hopes for the STELLAR trial. Prior to the ECLIPSE failure, Isaacs told Scrip in an interview that “We all hope the ECLIPSE trial is positive, and we think it will be, but we think STELLAR will be even better.”

Sonnier noted that overall survival for advanced pancreatic cancer patients treated with standard-of-care chemotherapy combinations is six to eight months, so STELLAR will have to exceed that to prove the value of CRS-207 and GVAX in combination with Opdivo.

In addition to STELLAR, Aduro is testing CRS-207 plus Incyte’s epacadostat in a Phase I/II clinical trial called SEASCAPE, which began in March to evaluate the combination in up to 126 women with platinum-resistant ovarian, fallopian or peritoneal cancers. Aduro is funding the trial, but Incyte is supplying its drug for the study; neither firm has any rights to the other company’s asset.

Beyond The 10 Key Targets, But Still Combined With PD-1

Armo BioSciences Inc. has a fresh perspective on immuno-oncology outside of key targets like PD-1 and IDO. The company is developing pegylated formulations of recombinant human interleukins, starting with lead program AMO010, a pegylated Interleukin 10 (IL-10) that’s being studied in a Phase I/Ib clinical trial. ARMO’s $50m Series C venture capital round, which closed in February, will fund a Phase II/III trial and support clinical development of pegylated versions of additional cytokines – IL-12 and IL-15. (Also see “ARMO Rides Immuno-Oncology Wave With $50m For Its PD-1 Booster” - Scrip, 17 Feb, 2016.)

The drug candidates are designed to boost the activity of PD-1 inhibitors and other first-generation immuno-oncology therapies. A cytokine, such as a pegylated interleukin, should cause the immune system to produce more T-cells, so that the immune system is more fully activated upon administration of an anti-PD-1 therapy or chemotherapy.

The combination could make PD-1 inhibitors viable treat-
ments for cancers in which they are not particularly effective as a monotherapy, such as pancreatic, triple-negative breast and colorectal cancers. ARMO is testing AM0010 with approved PD-1 inhibitors, but the company is developing its own anti-PD-1 therapy that it plans to study in combination with its pegylated IL-15 in a Phase I trial that could kick off in 2017.

Data from 24 patients with advanced pancreatic cancer who were treated with AM0010 alone or with chemotherapy and 16 patients with colorectal cancer who received AM0010 monotherapy will be presented in a poster session during ASCO on June 5. Four patients achieved greater than six months of progression-free survival. The median overall survival among 20 pancreatic cancer patients was 5.1 months, while median overall survival was 15.4 months for 13 colorectal cancer patients.

Data also will be presented on June 5 at ASCO in a poster for AM0010 in combination with a PD-1 inhibitor, including objective responses observed in four out of eight renal cell carcinoma, two out of five NSCLC patients, and two out of six melanoma patients.

ARMO and its IL-10-targeting therapy could be a surprise hit at the ASCO meeting, although as a private company it has no stock price to indicate what investors think of the data. Even so, stock analysts are watching ARMO’s early results to see whether the IL-10 data live up to early expectations.

Leerink analyst Seamus Fernandez described the ARMO data as the “most interesting” combination immunotherapy results that will be presented during the ASCO meeting.

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Fix Antibiotic Payment Models To Spur R&D Investment, US FDA’s Gottlieb Says

By Sue Sutter

US FDA Commissioner Scott Gottlieb is making the case for reimbursement changes aimed at spurring investment and development in new antimicrobials for multi-drug resistant pathogens. Citing the need for more “pull” incentives to attract R&D investment in the space, Gottlieb discussed a potential reimbursement model in which hospitals would pay a subscription-based fee for access to approved antibiotics targeted at hard-to-treat infections.

FDA is talking to the Centers for Medicare and Medicaid Services (CMS) about such an approach and the potential for a demonstration project, Gottlieb said, suggesting that the US regulatory agency could have a role in defining the parameters for when a new antimicrobial might qualify for this type of payment system.

Gottlieb’s remarks came during a Sept. 14 event at the Pew Charitable Trusts in Washington, DC, where the commissioner discussed the FDA’s efforts to combat antimicrobial resistance.

“The economics of this category and our public health prerogatives are not entirely in sync.”
resistance and promote the development of new anti-infective agents.

**Stepping Into The Reimbursement Ring, Again**

Medical product reimbursement is not an issue directly within the FDA’s regulatory purview. However, when payment models do not provide adequate return on investment, the result is a decline in both R&D investment and drug applications crossing the agency’s desk.

In public remarks, Gottlieb repeatedly has cited the need for more innovative reimbursement models to spur market competition and lower prices – as in the case of biosimilars – or to encourage R&D investment in new therapies for hard-to-treat conditions. (Also see “FDA Commissioner’s Rx For US Biosimilars Market: Reform Contracting Practices And Payment Models” - Scrip, 19 Jul, 2018.)

Like other experts in the field of antibiotic development, the commissioner cited the need for both “push” incentives, designed to directly support product R&D, and “pull” incentives, aimed at rewarding products that reach market and ensuring an adequate return on investment. (Also see “New Report Calls For Pushing And Pulling In Global Fight Against Superbugs” - Scrip, 24 Jan, 2018.)

“A lot of the focus, so far, has been placed on developing push incentives,” he said. “I think much more emphasis needs to be placed on developing pull incentives. These can create natural markets for drugs targeted to rare but dangerous, multi-drug resistant pathogens that can threaten human health.”

Most large pharmaceutical companies have abandoned antibiotic drug development, Gottlieb noted (see sidebar). “While some small, venture-backed, start-up companies remain engaged, these companies are not as well positioned to fund the larger confirmatory trials required for regulatory approval,” he said.

FDA would like to see “a balanced level of investment, and more interest in these opportunities. We’d like to see a more robust market for these products, complemented by a robust pipeline.”

However, the market dynamics for antibiotics are problematic because under current reimbursement systems profits are driven by the number of prescriptions written for a drug. Yet, when a new antibiotic is aimed at treating multi-drug resistance, the therapeutic is justifiably held in reserve until absolutely necessary, he said.

“‘In other words, the reimbursement scheme is in direct conflict to our public health goals,’ he said, in effect removing the market incentives for antibiotic development.

Another commercial challenge lies in the fact that generic antibiotics are inexpensive and widely effective first-line treatments, Gottlieb said, adding that that Medicare’s in-patient prospective payment system for hospital care is pegged to the price of generics.

“Novel drugs eat into the profits of hospitals. And when new and better antibiotics are available, these novel drugs are reserved for last-line cases when their unique profiles, and higher prices, are justified because first-line drugs have failed,” Gottlieb said. “This is completely justifiable behavior. If a new product is overused, it can reduce effectiveness by increasing antimicrobial resistance.”

However, keeping a drug in reserve also shrinks product revenues early in a drug’s patent life. “The economics of this category and our public health prerogatives are not entirely in sync,” he said.

“If we want to maintain a robust pipeline for antibiotics, it is necessary to change the perception that the costs and risks of antibiotic innovation are too high relative to their expected gains – without weakening antibiotic stewardship,” he said. “It is important to pursue new policies and reimbursement approaches now, to shift the investment landscape right away.”

**Foundation For Return On Investment**

What’s needed, Gottlieb said, are reimbursement reforms that allow innovators to capture up front more of the long-run, social and economic value generated from the development of new antibiotics.

Such reforms could include a mix of milestone payments and subscription fees for developers of FDA-approved products with high economic and clinical value that are
targeted at multi-drug resistant organisms and linked to proven clinical outcomes.

“A subscription-based model could see hospitals paying a flat rate for access to a certain number of doses of an important new antimicrobial,” he said. “These subscription fees could be priced at a level to create a sufficient return on the investment to develop drugs with a certain profile. This should have the effect of creating a natural market for drugs that meet certain important specifications.”

“The goal would be to have a subscription-based model for big institutions that are most likely to use drugs targeted to multi-drug resistant organisms that would provide sort of a foundation of return on investment.”

However, the subscription model would not encompass the whole market for a particular drug. “The goal would be to have a subscription-based model for big institutions that are most likely to use drugs targeted to multi-drug resistant organisms that would provide sort of a foundation of return on investment,” he said.

Hospitals already employ this type of reimbursement model for software and durable medical equipment, but not for drugs, Gottlieb said. “Hospitals are used to paying for things on a subscription-based model where they pay a flat fee for access to something and they might pay a variable fee based on the number of beds they have or the number of admissions they have, or for a certain number of uses.”

Gottlieb said he has talked to CMS and its Center for Medicare and Medicaid Innovation (CMMI) about alternative payment models for antimicrobials but noted it’s still too early to say whether a demonstration project could be performed thought CMMI.

However, he suggested that non-governmental entities, such as the Gates Foundation and commercial insurers, also could test innovative payment approaches.

The FDA, in turn, could play a role in “helping to define the parameters of what such a drug would look like, and if a drug meets those parameters then the reimbursement mechanism would pay for it under a different approach that would be more of a subscription model,” Gottlieb said. “So we provide a very clear, upfront incentive for trying to develop drugs that have these kinds of profiles.”

A Better Option Than Stockpiling
Innovative payment models would be more likely to encourage R&D investment than the potential for government stockpiling of new antimicrobials, Gottlieb said.

Decisions on medical product stockpiling are generally based on national security considerations, in contrast to the clinical context that surrounds antibiotic use, he said. “I don’t think that stockpiling alone creates a sustained natural market for a product that is going to create the kinds of incentives for development that we want to see.”

Referencing his work as an industry consultant in the years before he assumed the role of FDA commissioner, Gottlieb said, “I’ve been on the other side of this … and I’ve seen discussions in board rooms and elsewhere around whether or not a certain product might meet the profile of something that would be stockpiled as part of a strategic decision.”

“That was rarely, if ever in my travels, the pivot that made the decision to make an investment,” he said. “It was a nice to have. It wasn’t the point at which you made an investment decision, because … that was always a binary decision. You weren’t sure if the government was going to stockpile it, you weren’t sure how much they would stockpile, you weren’t sure how much that stockpile would turn over.”

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